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**Citation for published version:**

Rzechorzek, NM, Connick, P, Livesey, M, Borooah, S, Patani, R, Burr, K, Story, D, Wyllie, D, Hardingham, G & Chandran, S 2016, 'Hypothermic modulation of human cortical neurons to explore a role for tau protein in neuroprotection', *The Lancet*, vol. 387, pp. S88.

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Publisher's PDF, also known as Version of record

**Published In:**

The Lancet

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# Hypothermic modulation of human cortical neurons to explore a role for tau protein in neuroprotection

Nina M Rzechorzek, Peter Connick, Matthew R Livesey, Shyamanga Borooah, Rickie Patani, Karen Burr, David Story, David J A Wyllie, Giles E Hardingham, Siddharthan Chandran

## Abstract

Published Online  
February 25, 2016

Poster 44

Centre for Clinical Brain  
Sciences, University of  
Edinburgh, Edinburgh,  
UK (N M Rzechorzek PhD,  
Prof S Chandran PhD);

MRC Centre for Regenerative  
Medicine, University of  
Edinburgh, Edinburgh,  
UK (N M Rzechorzek,  
S Borooah MRCP(UK),  
K Burr PhD, D Story BSc,  
Prof S Chandran);

Anne Rowling Regenerative  
Neurology Clinic, University of  
Edinburgh, Edinburgh,  
UK (P Connick PhD, S Borooah,  
R Patani PhD, Prof S Chandran);  
Euan MacDonald Centre for  
MND Research, University of  
Edinburgh, Edinburgh,  
UK (N M Rzechorzek,  
M R Livesey PhD, S Borooah,  
K Burr, D Story,  
Prof D J A Wyllie PhD,  
Prof S Chandran); Centre for  
Integrative Physiology,  
University of Edinburgh,  
Edinburgh, UK (M R Livesey,  
Prof D J A Wyllie,  
Prof G E Hardingham PhD); and  
Institute of Neurology,  
University College London,  
London, UK (R Patani)

Correspondence to:  
Dr Nina M Rzechorzek, Centre for  
Clinical Brain Sciences,  
University of Edinburgh,  
Chancellor's Building,  
Edinburgh EH16 4BS, UK  
nina.rzechorzek@ed.ac.uk

The full paper is published in  
eBiomedicine <http://dx.doi.org/10.1016/j.ebiom.2015.12.010>

**Background** Cooling is the single most effective treatment for acute neuronal injury. Understanding the molecular mechanisms that mediate cooling-induced neuroprotection might yield novel therapeutic targets for neurodegenerative disease. Many of these disorders involve modulation of tau, a protein that is enriched in neurons and becomes hyperphosphorylated in hypothermic, injury-resistant rodent brains as well as in Alzheimer's disease. We sought to establish a new model for exploring human tau physiology and its role in neuroprotection in the context of therapeutic hypothermia.

**Methods** Functional cortical neurons (hCNs) were differentiated from three independent human pluripotent stem-cell lines and validated for regional identity and tau status. Matched cultures were incubated at 37°C or clinically targeted temperatures for therapeutic hypothermia (32°C) and suspended animation (28°C). Effects of cooling on tau status and neuronal injury elicited by common neurotoxic stressors were established. Injury experiments were repeated while manipulating tau phosphorylation.

**Findings** hCN differentiation featured transitions in tau status, recapitulating transcriptional and post-translational human in-vivo cortical tau development. Key aspects of this development were reversed by cooling. Notably, cooling induced tau hyperphosphorylation via rapid inhibition of the major tau phosphatase, protein phosphatase 2A (PP2A). Multiplexed injury analysis confirmed that hypothermia robustly protected hCNs from oxidative (100 µM hydrogen peroxide) and excitotoxic (30 µM glutamate) stress (at 28°C, injury was reduced by 78% and 56%, respectively;  $p < 0.0005$ ). Selective block of a major tau kinase reduced hCN tau phosphorylation and abrogated hypothermic protection ( $p = 0.001$ ) against oxidative injury at 28°C (injury reduction diminished to 9% at 100 µM hydrogen peroxide), whereas pharmacological inhibition of PP2A mimicked cooling-induced tau phosphorylation and protected hCNs from oxidative injury at 37°C (up to 22% injury reduction [ $p = 0.008$ ], with no benefit under hypothermic conditions).

**Interpretation** To our knowledge, this is the first study of human neuronal tau physiology under hypothermic conditions. Although definitive experiments are needed, our findings support previous work linking phospho-tau to neuroprotection. Furthermore, cold-induced tau hyperphosphorylation is a potential trigger for proteostatic priming, a recently discovered mechanism of hypothermic preconditioning in hCNs. Exploiting these cryobiological effects might lead to new treatments for acute and chronic neuronal injury.

**Funding** Wellcome Trust, Anne Rowling Regenerative Neurology Clinic, Euan MacDonald Centre for Motor Neurone Disease Research.

## Contributors

NMR conceived the study, devised the methodology, conducted investigations, analysed the data, acquired funding and resources, and wrote the first draft of the abstract. PC devised the methodology, analysed the data, acquired funding and resources, and reviewed and edited the abstract. MRL conducted investigations, analysed the data, and reviewed and edited the abstract. RP, DS, and KB reviewed and edited the abstract. SB and DJAW acquired resources and reviewed and edited the abstract. GEH and SC acquired funding and resources, reviewed and edited the abstract, and supervised the study.

## Declaration of interests

We declare no competing interests.